NONTECHNICAL ABSTRACT

Interleukin-12 (IL12) is a protein product of monocytes and macrophages which has been shown in animal studies to produce tumor regression by enhancing immune responses directed against tumor cells. The recombinant IL12 protein has been administered to patients with advanced cancer, and has been found to be toxic at higher doses with limited antitumor efficacy.

We have shown in mice bearing established tumors in their livers that gene therapy by intratumoral injection of an adenoviral vector (ADV-mIL12) expressing murine interleukin-12 was effective in producing tumor regression and survival prolongation, with 20-40% of treated animals alive at 160 days compared to control animals which all died by 75 days. The treatment was also well tolerated without serious adverse effects at therapeutically effective doses of the vector. When ADV-mIL12 was administered at higher doses, toxicities similar to those of the recombinant IL12 protein were seen.

We have translated these preclinical findings into two Phase I trials proposed in this IND application. Both trials aim to evaluate the safety of adenoviral vector expressing human IL12 (ADV-hIL12) when administered by intratumoral injection in patients with tumors in the liver. One trial will study patients with metastatic breast cancer to the liver, while the other will evaluate patients with metastatic non-breast or primary malignant tumors in the liver. The intratumoral injection is performed by percutaneous insertion of up to three skinny needles through the skin into one liver tumor under ultrasound guidance. The dose of ADV-hIL12 will be escalated in half log increments in seven cohort levels from 1×10^8 to 1×10^{12} pfu, with three patients per dose level cohort. The starting dose is four logs of magnitude below the equivalent dose by body weight which has been shown to be well tolerated in mice. We will also collect data on the effectiveness of the treatment in producing tumor regression and in inducing immune responses.

Clinical grade ADV-hIL12 has been produced for use in the proposed clinical trials by the University of Pennsylvania Institute for Human Gene Therapy. The trial in metastatic breast cancer is sponsored by the U.S. Army Medical Research Acquisition Activity (Grant No. DAMD17-98-1-8322), while the other trial in patients with metastatic nonbreast or primary cancers in the liver is sponsored by the Mount Sinai School of Medicine.